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Synthesis of Antiviral Nucleosides from Crotonaldehyde. Part 3.[1,2] Total Synthesis of Didehydrodideoxythymidine (d4T)

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Abstract: The total synthesis of the antiviral agent d4T **3** from the epoxyalcohol **2**, itself derived from crotonaldehyde **1**, in 6 steps and 18% overall yield is described.

Inhibition of viral reverse transcriptase is currently the most established effective point of intervention for the treatment of retroviral diseases such as AIDS. Modified 2'-deoxynucleosides lacking a 3'-hydroxyl group are often good inhibitors of HIV reverse transcriptase, and thus exhibit anti-HIV activity. These include the currently approved therapies for AIDS or ARC, 3'-azido-3'-deoxythymidine (AZT),[3] and dideoxyinosine, ddI[4,5], and several other drugs currently in clinical trials as anti-AIDS drugs, including ddC.[6]

The modified nucleoside didehydrodideoxythymidine, d4T, **3**, is also attracting current interest as another potentially clinically useful anti-HIV agent.[7] AZT insensitive HIV strains do not show cross resistance to d4T,[8] and d4T readily crosses the blood brain barrier.[9] Furthermore, its lower toxicity than, and comparable potency to, AZT suggest considerable potential for d4T as an anti-AIDS drug.[10] A number of syntheses from nucleoside starting materials,[11] or from carbohydrate derived materials such as ribonolactone,[12] have been reported, but no synthesis to date has commenced from non-chiral pool materials.

As part of our program to develop novel and versatile synthetic routes to modified nucleosides,[13] we have recently reported the syntheses of the anti-AIDS drug AZT,[1] and of the anti-HIV agent ddC,[2] each in nine steps from the inexpensive achiral starting material, crotonaldehyde, **1**. Chirality was introduced by a Sharpless-Katsuki asymmetric epoxidation to give the common chiral epoxy alcohol, **2**.

We now report that the epoxy alcohol, **2**, can also be elaborated in six steps to the anti-HIV agent, d4T (**3**), (Scheme I), and also to the 5'-acetyl-3'-thiophenylthymidine, **8a**, and 5'-acetyl-3'-selenophenylthymidine, **8b**, nucleoside analogues in four steps from **2**.

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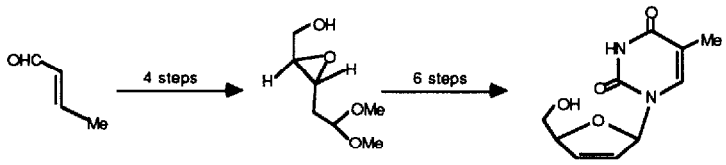


1 2 3 d4T

Scheme I

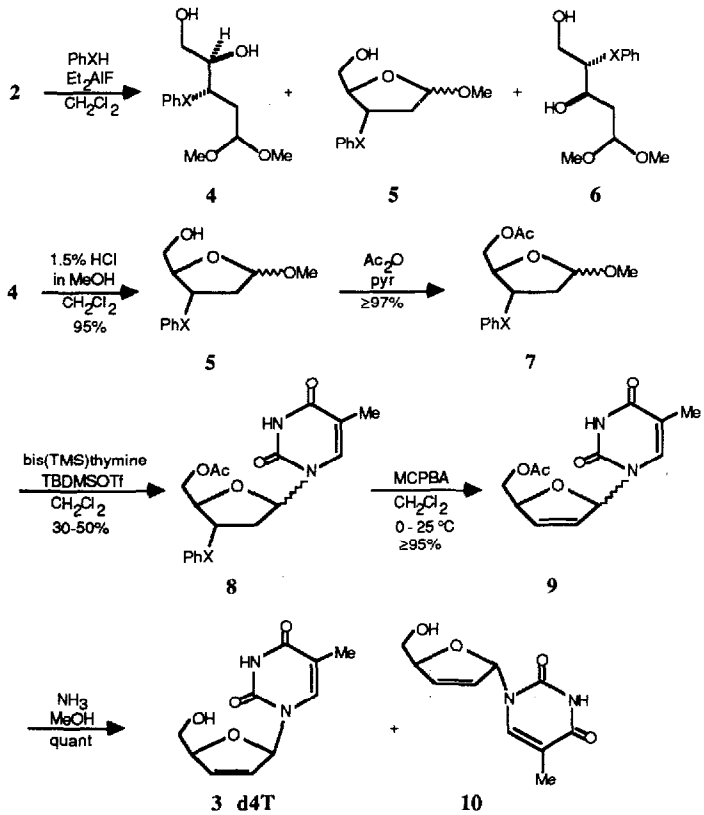
Ring opening of the epoxy alcohol **2** with either thiophenol or selenophenol (1 equiv), was catalysed by diethylaluminum fluoride (other Lewis acids were ineffective), affording mixtures of the anticipated 1,2-diol products, **4**, (major product; 50% X = S; 30% X = Se), together with 8-10% of the undesired 1,3-diols, **6**, and 9-11% of the methyl glycosides, **5**. The minor products were separated from the major diol by either flash chromatography or preparative tlc. Cyclization of the diols **4** to the glycosides **5** proceeded in near quantitative yield, by employment of the conditions utilized previously in our syntheses of AZT[1] and ddC.[2] Combination of the glycosides (**5**) obtained from this reaction and from concomitant cyclization during the ring opening reaction, therefore affords **5a** and **5b** from epoxyalcohol **2** in overall yields of 48% and 29% respectively.

Acetylation of these alcohols to give the acetates **7** proceeded in ≥97% yield, after chromatography. Vorbrüggen coupling[14] of these acetates with 2-3 equivalents of bis(trimethylsilyl)thymine catalysed by 2-3 equivalents of *t*-butyldimethylsilyl triflate (TBDMSOTf) in acetonitrile, yielded the 5'-acetyl-3'-thiophenylthymidine, (**8a**) and 5'-acetyl-3'-selenophenylthymidine, (**8b**), in 30% and 50% yields respectively, as anomeric mixtures.[12c,d]

Treatment of the seleno compound, **8b**, with 1 equivalent of *m*-chloroperoxybenzoic acid (MCPBA) in dichloromethane at -5°C, and warming to room temperature over 2 hours, resulted in elimination of PhSeOH to give 5'-acetyl-d4T (**9**), in ≥95% yield.[15] Deacetylation was effected in quantitative yields by treatment with methanolic ammonia to provide d4T, **3**, and the α anomer, **10**, as a 1:1.5 mixture.[16] The ^{1}H NMR spectra of **9** and **3** matched those reported in the literature.[11a]

This route thus provides an anomeric mixture of d4T and its α anomer, **10**, in six steps and 18% overall yield from epoxyalcohol **2**, and in 10 steps and 5% overall yield from crotonaldehyde. We are currently attempting to separate the α and β anomers, d4T and **10**, and also the anomeric mixtures of d4T precursors **8** and **9**. The 5'-acetyl-3'-thiophenyl-thymidine (**8a**) and 5'-acetyl-3'-selenophenylthymidine (**8b**), are obtained in overall yields of 16% and 19% respectively from epoxy alcohol **2**.

The completion of this total synthesis, together with those of AZT[1] and ddC,[2] clearly establishes this methodology as a general and versatile strategy towards the efficient synthesis of a range of important antiviral modified nucleosides from cheap achiral starting materials. Further work on the extension of this methodology to other important types of modified nucleosides is underway.[17]



Scheme II. (a) X = S; (b) X = Se

Acknowledgment. We thank the National Institutes of Health (AI26692 and GM47228) and Burroughs-Wellcome for generous financial assistance, and the Royal Society (UK), Wellcome Trust, and SERC (UK) for travel grant assistance (to JMG).

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(13) For other strategies towards both C- and N-modified nucleosides from D-glucosamine, see: (a) Jung, M. E.; Trifunovich, I. D.; Gardiner, J. M.; Clevenger, G. L. *J. Chem. Soc. Chem. Commun.* **1990**, 84; (b) Jung, M. E.; Trifunovich, I. D. *Tetrahedron Lett.* **1992**, *33*, in press.

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(15) The appearance of the intermediate selenoxide while the reaction was cold, and its disappearance as elimination proceeded on warming, could be followed easily by tlc. A similar elimination on the 5'-TBDMS analogue of **8b** has recently been reported: see ref 12b.

(16) The anomers were not distinguishable by tlc.

(17) The diethyl analogue of our epoxy alcohol intermediate **4** has recently been shown by other workers to be a convenient intermediate towards the rapid synthesis of 4'-thio nucleosides: Uenishi, J.; Motoyama, M.; Nishiyama, Y.; Wakabayashi, S. *J. Chem. Soc. Chem. Commun.* **1991**, 1421.

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